Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma

Emily Y Kim1 Sophia Z. Shalhout2, David M. Miller2

1/9/23

# Featured Article

**Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma**. Rohaan et al. NEJM. 2022 Dec 8;387(23):2113-2125.

# Introduction

On January 9th, 2023, the multi-institutional Cutaneous Oncology Interest Group Journal Club reviewed the recently published NEJM article “Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma.”[1](#ref-Rohaan2022) Participants included clinicians and investigators from Massachusetts General Hospital, Brigham and Women’s Hospital, the National Institutes of Health, George Washington Medical Center, the University of Pittsburgh Medical Center and the Northwestern Feinberg School of Medicine. Importantly, the comments in this article represent the views of the authors of this Perspectives on the Science piece after the Journal Club. It does not represent views of any other members of the Interest Group or the affiliated institutions. In this article we provide a summary of the discussion regarding this important contribution to the literature.

# Background for the Study

Treatment options for melanoma have advanced greatly in the last several years and continue to evolve. Landmark studies such as KEYNOTE-001/006 and CheckMate-066 have led to immunotherapy with anti-PD-1 immune checkpoint inhibitors becoming first-line treatment options for advanced, unresectable melanoma (Figure 1).[2](#ref-Hamid2019)–[6](#ref-Petrella2017) CheckMate-067 reported a greater response rate with combination nivolumab plus ipilimumab, but greater adverse effects.[7](#ref-wolchok2017) Patients who have progressive disease on PD-1/PDL-1 therapy may have improved response or disease control on nivolumab plus relatlimab, a LAG-3 inhibitor.[8](#ref-tawbi2022),[9](#ref-long2022)

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| **Figure 1. Landmark studies in immune checkpoint inhibitor therapy for advanced melanoma.** |

If these treatment options fail, combined BRAF and MEK inhibition may be efficacious for melanomas with BRAF mutations, however, responses may not be sustained and resistance can develop.[10](#ref-robert2019a),[11](#ref-dummer2018) Despite these treatment measures, the 5 year mortality rate in patients with stage IV disease is 50%. Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) has shown clinical utility in melanoma since the 1990s.[12](#ref-rosenberg1994) In this process, tumor-resident T cells from a patient’s tumor are extracted and expanded ex-vivo. The patient is administered preparative lymphodepleting chemotherapy, often with cyclophosphamide and fludarabine, before the T-cells are infused back into the patient with interleukin-2 to further enhance in vivo expansion of cells and boost the antitumor response. While results have varied, multiple phase I and II trials have shown response rates around 50%.[13](#ref-vandenberg2020)–[20](#ref-Pilon-Thomas2012) Several of these studies are summarized in Figure 2. A recent study of LN-144 TIL therapy in patients who failed anti-PD-1 immunotherapy reported an objective response rate of 36%, highlighting potential utility of TIL therapy for patients who have had disease progression on first-line options.[21](#ref-Sarnaik2021)

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| **Figure 2. Summary of previous TIL studies in advanced melanoma.** |

# Study Design

This was a phase III, multicenter, open-label trial including patients age 18-75 with unresectable stage IIIC or IV melanoma. Patients were randomized in a 1:1 ratio to receive TIL or anti-cytotoxic T-lymphocyte antigen 4 therapy (ipilimumab). Patients assigned to the TIL group underwent a metastasectomy for retrieval and expansion of TILs, then received nonmyeloablative, lymphodepleting chemotherapy with cyclophosphamide and fludarabine. Single intravenous adoptive transfer of TILs was followed by high-dose interleukin-2 every 8 hours, for a maximum of 15 doses. Patients in the ipilimumab group received 3 mg per kilogram of body weight every 3 weeks, for up to 4 doses. The primary end point was progression-free survival, defined as the time from randomization to first disease progression or death. Secondary endpoints included progression-free survival (PFS), objective response, complete response, overall survival, health-related quality of life, and safety.

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| **Figure 3. Study design.** |

# Main Findings

168 patients (86% with disease refractory to anti–programmed death 1 treatment) were assigned to receive TILs (84 patients) or ipilimumab (84 patients). Median PFS in the TIL group was 7.2 months, significantly longer than 3.1 months in the ipilimumab group. Objective response rates were 49% in TIL group and 21% (95% CI, 13 to 32) of patients in ipilimumab group. 20% of patients in the TIL group achieved complete response, compared to 7% in the ipilimumab group. At the time of the data cutoff, the overall median follow-up was 33.0 months. Median overall survival was 25.8 months in the TIL group and 18.9 months in the ipilimumab group. In regards to safety, treatment related adverse events occurred in all patients in the TIL group and in 96% of those in the ipilimumab group. All patients in the TIL group experienced grade 3 adverse events, due to chemotherapy-related myelosuppression, while 57% of patients in the ipilimumab group experienced grade 3 or higher adverse events. Overall, patients in the TIL group had higher mean health-related quality of life scores than those in the ipilimumab group, though scores varied for different symptoms.

# Discussion Points

We began Journal Club by administering a poll among the attendees. Our goal was to conduct a brief survey before and after journal club discussions to determine the current practices of clinicians participating in the dialogue and how the current article might affect their practice. The attendees on January 9th, 2023 represented a diverse mix of clinical providers and non-clinical researchers (**Figure 4**).

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| **Figure 4. Journal Club Attendees** |

In order to begin a conversation about the evolving approach to advanced melanoma, attendees were queried as to how they would have likely managed a case of ICI-refractory melanoma, six months ago (**Figure 5**). Options included ipilimumab monotherapy, ipilimumab plus nivolumab, and ipilimumab plus relatlimab. Due to diverse nature of the COIG, 10 respondents felt comfortable making a treatment recommendation for regionally metastatic melanoma (6 members did not). Ninety percent (9/10) of the clinicians replied that six-months ago they would have recommended combination CTLA-4/PD-1 directed therapy for PD-1 refractory disease. Given the patient’s ECOG status of 2, one respondent would have recommended combination CTLA-4/LAG-3 in this case.

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| **Figure 5. Management Strategies of ICI-refractory melanoma** |

Respondents were also queried as to whether or not they had every recommended TIL therapy previously as well as if their institutions had a cell therapy group with the capacity of delivering TIL therapy for melanoma. The majority of melanoma clinicians had previously recommended TIL therapy (**Figure 6**, 62%; 5/8) and were affiliates at institutions with a cell therapy group capable of delivery TIL therapy (**Figure 7**, 71%; 5/7).

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| **Figure 6. Experience with TIL Therapy** |

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| **Cell Therapy Capabilities** |

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| **Figure 7. Risk Benefit of Therapeutic Strategies for PD-1 Refractory Disease.** |

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| **Figure 8. Practice Changing Nature of the Study** |

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| **Figure 8. Case One Revisted** |

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| **Figure 9. Implementation of TIL Therapy** |

## Materials and Methods

This Perspectives on the Science piece was published using [Quarto](https://quarto.org)®. The survey was conducted using REDCap®.[22](#ref-Harris2009) The figures depicting the survey data were created using R (version 4.0.0) and the tidyverse suite of packages[23](#ref-tidyverse), including ggplot2[24](#ref-ggplot2) .

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# Author Affiliations

1. Brigham and Women’s Hospital, Boston MA
2. Mass General Cancer Center and Harvard Medical School, Boston MA
3. GW Cancer Center, George Washington University School of Medicine & Health Sciences, Washington DC
4. Pennsylvania Hospital and University of Pennsylvania, Philadelphia PA
5. Visiting Fellow in the Dermatology Branch at the National Institute of Arthritis and Musculoskeletal and Skin Diseases

## Disclosures

DMM reports grants and personal fees from Regeneron, grants from Kartos Therapeutics, grants from NeoImmuneTech, personal fees from Checkpoint Therapeutics, personal fees from Pfizer, personal fees from Merck Sharpe & Dome, personal fees from EMD Serono, grants from Project DataSphere, personal fees from Sanofi Genzyme, personal fees from Castle Biosciences, personal fees from Avstera, outside the submitted work. SZS reports no competing interests.

1. Rohaan, M. W. *et al.* [Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma](https://doi.org/10.1056/nejmoa2210233). *New England Journal of Medicine* **387**, 2113–2125 (2022).

2. Hamid, O. *et al.* [Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001](https://doi.org/10.1093/annonc/mdz011). *Annals of Oncology* **30**, 582–588 (2019).

3. Robert, C. *et al.* [Pembrolizumab versus Ipilimumab in Advanced Melanoma](https://doi.org/10.1056/nejmoa1503093). *New England Journal of Medicine* **372**, 2521–2532 (2015).

4. Robert, C. *et al.* [Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study](https://doi.org/10.1016/s1470-2045(19)30388-2). *The Lancet Oncology* **20**, 1239–1251 (2019).

5. Schachter, J. *et al.* [Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006)](https://doi.org/10.1016/s0140-6736(17)31601-x). *The Lancet* **390**, 1853–1862 (2017).

6. Petrella, T. M. *et al.* [Patient-reported outcomes in KEYNOTE-006, a randomised study of pembrolizumab versus ipilimumab in patients with advanced melanoma](https://doi.org/10.1016/j.ejca.2017.08.032). *European Journal of Cancer* **86**, 115–124 (2017).

7. Wolchok, J. D. *et al.* [Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma](https://doi.org/10.1056/nejmoa1709684). *New England Journal of Medicine* **377**, 1345–1356 (2017).

8. Tawbi, H. A. *et al.* [Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma](https://doi.org/10.1056/nejmoa2109970). *New England Journal of Medicine* **386**, 24–34 (2022).

9. Long, G. V. *et al.* [Relatlimab and nivolumab versus nivolumab in previously untreated metastatic or unresectable melanoma: Overall survival and response rates from RELATIVITY-047 (CA224-047)](https://doi.org/10.1200/jco.2022.40.36_suppl.360385). *Journal of Clinical Oncology* **40**, 360385–360385 (2022).

10. Robert, C. *et al.* [Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma](https://doi.org/10.1056/nejmoa1904059). *New England Journal of Medicine* **381**, 626–636 (2019).

11. Dummer, R. *et al.* [Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF -mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial](https://doi.org/10.1016/s1470-2045(18)30142-6). *The Lancet Oncology* **19**, 603–615 (2018).

12. Rosenberg, S. A. *et al.* [Treatment of Patients With Metastatic Melanoma With Autologous Tumor-Infiltrating Lymphocytes and Interleukin 2](https://doi.org/10.1093/jnci/86.15.1159). *JNCI Journal of the National Cancer Institute* **86**, 1159–1166 (1994).

13. Berg, J. H. van den *et al.* [Tumor infiltrating lymphocytes (TIL) therapy in metastatic melanoma: boosting of neoantigen-specific T cell reactivity and long-term follow-up](https://doi.org/10.1136/jitc-2020-000848). *Journal for ImmunoTherapy of Cancer* **8**, e000848 (2020).

14. Dudley, M. E. *et al.* [Adoptive Cell Therapy for Patients With Metastatic Melanoma: Evaluation of Intensive Myeloablative Chemoradiation Preparative Regimens](https://doi.org/10.1200/jco.2008.16.5449). *Journal of Clinical Oncology* **26**, 5233–5239 (2008).

15. Rosenberg, S. A. *et al.* [Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using T-Cell Transfer Immunotherapy](https://doi.org/10.1158/1078-0432.ccr-11-0116). *Clinical Cancer Research* **17**, 4550–4557 (2011).

16. Besser, M. J. *et al.* [Clinical Responses in a Phase II Study Using Adoptive Transfer of Short-term Cultured Tumor Infiltration Lymphocytes in Metastatic Melanoma Patients](https://doi.org/10.1158/1078-0432.ccr-10-0041). *Clinical Cancer Research* **16**, 2646–2655 (2010).

17. Ellebaek, E. *et al.* [Adoptive cell therapy with autologous tumor infiltrating lymphocytes and low-dose Interleukin-2 in metastatic melanoma patients](https://doi.org/10.1186/1479-5876-10-169). *Journal of Translational Medicine* **10**, (2012).

18. Andersen, R. *et al.* [Long-Lasting Complete Responses in Patients with Metastatic Melanoma after Adoptive Cell Therapy with Tumor-Infiltrating Lymphocytes and an Attenuated IL2 Regimen](https://doi.org/10.1158/1078-0432.ccr-15-1879). *Clinical Cancer Research* **22**, 3734–3745 (2016).

19. Dudley, M. *et al.* A phase i study of nonmyeloablative chemotherapy and adoptive transfer of autologous tumor antigen-specific t lymphocytes in patients with metastatic melanoma. *Journal of Immunotherapy* (2022) doi:[10.1097/01.CJI.0000016820.36510.89](https://doi.org/10.1097/01.CJI.0000016820.36510.89).

20. Pilon-Thomas, S. *et al.* [Efficacy of Adoptive Cell Transfer of Tumor-infiltrating Lymphocytes After Lymphopenia Induction for Metastatic Melanoma](https://doi.org/10.1097/cji.0b013e31826e8f5f). *Journal of Immunotherapy* **35**, 615–620 (2012).

21. Sarnaik, A. A. *et al.* [Lifileucel, a Tumor-Infiltrating Lymphocyte Therapy, in Metastatic Melanoma](https://doi.org/10.1200/jco.21.00612). *Journal of Clinical Oncology* **39**, 2656–2666 (2021).

22. Harris, P. A. *et al.* [Research electronic data capture (REDCap)A metadata-driven methodology and workflow process for providing translational research informatics support](https://doi.org/10.1016/j.jbi.2008.08.010). *Journal of Biomedical Informatics* **42**, 377–381 (2009).

23. Wickham, H. *et al.* [Welcome to the tidyverse](https://doi.org/10.21105/joss.01686). **4**, 1686 (2019).

24. Wickham, H. [*ggplot2: Elegant graphics for data analysis*](https://ggplot2.tidyverse.org). (Springer-Verlag New York, 2016).